REMARKS

Claim 1 has been amended to recite "[a] process for the biological production of vitamin B_6 which comprises cultivating a host cell transformed or transfected by an isolated DNA or by a vector or plasmid comprising the isolated DNA under conditions conducive to the production of vitamin B_6, and recovering vitamin B_6 from the culture, wherein the host cell is selected from Sinorhizobium or Escherichia and wherein the isolated DNA comprises a nucleotide sequence encoding PdxR, which is a flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase, selected from the group consisting of:

(a) a DNA sequence identified by SEQ ID NO:1 or the complementary strand thereof;

(b) a DNA sequence which hybridizes under stringent hybridization and stringent washing conditions to the DNA sequence complementary to the DNA sequence defined in (a), and encodes a polypeptide having the activity of flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase;

(c) a DNA sequence encoding a polypeptide having the amino acid sequence encoded by the DNA sequence of (a) or (b);

(d) a DNA sequence which is at least 80% identical to a DNA encoding a polypeptide which comprises the amino acid sequence of SEQ ID NO: 2, and encodes a polypeptide having the activity of flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase; and

(e) a DNA sequence encoding a polypeptide which comprises an amino acid sequence which is at least 80% identical to the amino acid sequence of SEQ ID NO: 2,

and encodes a polypeptide having the activity of flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase." Support for these amendments is found in original claims 1 and 3 and in the specification at, for example, page 1, lines 15-21, page 2, lines 5-14, page 3, lines 18-19, page 4, lines 27-33, and in Examples 1-4. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01 (o) and (l).

Claim 2 has been amended to recite "[a] process for the biological production of vitamin B_6 which comprises introducing the isolated DNA as claimed in any one of (a) to (e) in claim 1 into an appropriate host cell selected from Sinorhizobium melioti or Escherichia coli, cultivating the obtained host cell under conditions conducive to the production of vitamin B_6, and recovering vitamin B_6 from the culture." Support for these amendments is found in original claims 1 and 3 and in the specification at, for example, page 1, lines 15-21, page 2, lines 5-14, and in Examples 1-4. (*Id.*).

Claim 3 has been amended to depend from claim 1 only.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

PRIORITY:

We thank the Examiner for his acknowledgment "of applicant's claim for foreign priority of EP 02021641.2." (Paper No. 20060907 at 2). The Examiner stated, however, "that the current claims have not been granted the benefit of the claimed priority date because there is no support for the claimed invention in the *provisional application*." (*Id.*). The Examiner is *mistaken*. This application does not claim benefit to a *provisional application*. This application is the National Stage of International Application No. PCT/EP2003/010684, filed September 25, 2003. The international

application claims benefit to EP 02021641.2. The currently pending application is identical to the priority document, EP 02021641.2. Accordingly, there can be no question that the present application ***is*** entitled benefit back to the filing date of EP 02021641.2.

Therefore, for the reasons set forth above, it is submitted that Applicants have complied with all rules regarding priority under 35 U.S.C. § 119, and it is requested that the Examiner confirm on the record that the claim to benefit has been perfected.

OBJECTIONS:

Claims 1 and 2 have been objected to because the term "conductive" should be "conducive." (Paper No. 20060907 at 2).

As suggested by the Examiner, and with a view towards furthering prosecution, claims 1 and 2 have been amended to recite "conducive" instead of "conductive." In view of the foregoing amendments, the objection of claims 1 and 2 is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

Claim 1 has also been objected to because of the phrases "that encodes" and "which encodes for." (Paper No. 20060907 at 2).

As suggested by the Examiner, and with a view towards furthering prosecution, claim 1 has been amended to recite "encoding" instead of "that encodes" and "which encodes for." In view of the foregoing amendments, this objection of claim 1 is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

§112, SECOND PARAGRAPH REJECTIONS:

Claims 1-3 have been rejected under 35 U.S.C. §112, second paragraph. (Paper No. 20060907 at 3).

In making the rejection, the Examiner asserted that "[c]laim 1 is indefinite in the recitation 'to the extent of at least 80%.'" (*Id.*).

With a view towards furthering prosecution, claim 1 has been amended to recite "at least 80%." In view of the foregoing amendment, the rejection of claim 1 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

The Examiner also asserted, with respect to claim 1, that the phrase "hybridizes under standard conditions" is indefinite because "the specification does not define what conditions constitute 'standard.'" (*Id.*).

We respectfully note that the Examiner's conclusion that the specification does not define "what conditions constitute standard" is in error. The hybridization and wash conditions are clearly disclosed at, *e.g.*, page 3, lines 15-21 of the specification. Based on this disclosure and with a view towards furthering prosecution, claim 1 has been amended to recite "stringent hybridization and stringent washing conditions." In view of the foregoing, the rejection of claim 1 (and dependent claims 2-3) is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

§112, FIRST PARAGRAPH REJECTION:

Enablement

Claims 1-3 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. (Paper No. 20060907 at 4). In making the rejection, the Examiner acknowledged that "the specification ... [is] enabling for a process for the biological

production of vitamin B6 comprising cultivating a Sinorhizobium cell transformed or transfected by a DNA molecule of SEQ ID NO: 1 from S. meliloti encoding a polypeptide of SEQ ID NO: 2 having D-erythronate-4-phosphate dehydrogenase activity." (*Id.*).

The Examiner, however, asserted that "the specification ... does not reasonably provide enablement for a process for the biological production of vitamin B6 comprising cultivating ***any*** host cell transformed or transfected by ***any*** DNA molecule or a fragment thereof, encoding ***any*** polypeptide having D-erythronate-4-phosphate dehydrogenase activity or any DNA molecule, which is 80% identical to SEQ ID NO: 1 encoding any polypeptide which is 80% identical to SEQ ID NO: 2 having flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase activity." (*Id.*) (emphasis added).

Initially, we note it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry his/her burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370. It is well established that claims must be separately analyzed. *Ex parte Jochim*, 11 USPQ2d 561 (BPAI 1988).

In particular, claim 1 now recites that the host cell that is selected from "Sinorhizobium or Escherichia." Moreover, claim 1 is specifically tied to a recited function, namely "a flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase." And, claim 1 has been amended to recite DNA sequences that

hybridize under ***stringent*** hybridization and wash conditions to SEQ ID NO: 1 or its complement ***and*** that have the function of "flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase." With these amendments, it is respectfully submitted that the Examiner's concerns regarding the scope of claim 1, *i.e.*, "***any*** host cell transformed or transfected by ***any*** DNA molecule or a fragment thereof, encoding ***any*** polypeptide having D-erythronate-4-phosphate dehydrogenase activity ..." is rendered moot. (Paper No. 20060907 at 4) (emphasis added).

Moreover, as is well accepted, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. MPEP § 2164.05 and *In re Wands*, 8 USPQ at 1404. In addition, "a patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01 (8th ed. Rev. 5, August 2006, p. 2100-187) *citing In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In this regard, we note that the specification provides ample disclosure sufficient to inform a skilled artisan that the Applicants enabled the currently claimed process for the biological production of vitamin B6. For example, the specification discloses four detailed examples and five tables that provide sufficient instruction to one skilled in the art on how to make and use the currently claimed process.

Specifically, the specification discloses, *inter alia*, the nucleotide sequence of the identified PdxR gene (SEQ ID NO: 1), assays to test the function of putative

PdxR enzymes, specific stringent hybridization conditions, and host cells useful for the production of vitamin B6 for identifying enzymes which would fall under the currently claimed process. (*See, e.g.,* Specification at page 1, lines 15-21, page 2, lines 5-14, page 3, lines 18-19, page 4, lines 27-33, and in Examples 1-4).

Thus, the specification discloses how to isolate, identify, and use the PdxR enzymes according to the presently claimed process of the present invention. (*See, e.g.*, pages 7-11 of Example 1). Indeed, identifying the DNA sequences capable of encoding PdxR according to the amended process claims is a matter of applying the disclosure in the specification of how to make or isolate such an enzyme and testing the enzyme in a host cell and comparing the levels of vitamin B6 produced by the transformed host cell to the unmodified host microorganisms. (*See* Table 5). It is respectfully submitted that such activity is not undue experimentation.

For the reasons set forth above, it is respectfully submitted that the rejection has been rendered moot and should be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103:

Claims 1-2 have been rejected under 35 U.S.C. § 103 as being unpatentable over Capela, D. *et al.* Database SWALL Database Abstract No. XP-002266688 (2001) ("Capela") and Capela, D. *et al. "Analysis of the Chromosome Sequence of the Legume Symbiont Sinorhizobium meliloti Strain 1021,"* Proc. Natl. Acad. Sci., v. 98, no. 17, pp. 9877-9882 (2001) ("Capela II") in view of Yocum *et al.*, U.S. Patent Publication No. 2005/0164335 ("Yocum"). (Paper No. 20060907 at 7).

The rejection respectfully is traversed.

Capela discloses an amino acid sequence for "a putative oxidoreductase protein." (Capela).

Capela II discloses that "*Sinorhizobium meliloti* is an α-proteobacterium that forms agronomically important N_2-fixing root nodules in legumes." (Page 9877). Capela II further discloses "the complete sequence of the largest constituent of its genome, a 62.7% CG-rich 3,654,135-bp circular chromosome." (*Id.*). Capela II also discloses that "[a]nnotation allowed assignment of a function to 59% of the 3,341 predicted protein-coding ORFs, the rest exhibiting partial, weak, or no similarity with any known sequence," and that "the level of reiteration within this replicon is low, with only two genes duplicated with more than 90% nucleotide sequence identity, transposon elements accounting for 2.2% of the sequence, and a few hundred short repeated palindromic motifs (RIME1, RIME2, and C) widespread over the chromosome." (*Id.*).

Yocum discloses "methods of producing B6 vitamers that involve culturing an organism overexpressing an enzyme that catalyzes a step in the biosynthesis of a B6 vitamer under conditions such that a B6 vitamer is produced." (Abstract). Yocum further discloses "methods of producing B6 vitamers that involve culturing recombinant microorganisms having increased activity of at least one B6 vitamer biosynthetic enzyme, *e.g.*, YaaD or YaaE, or a homologue thereof, or Epd, PdxA, PdxJ, PdxF, PdxB, PdxH, and/or Dxs, or a homologue thereof." (*Id.*).

In making the rejection, the Examiner asserted that Capela discloses "a putative oxidoreductase protein, which is 100% identical to SEQ ID NO: 2 of the instant application, inherently a[n] erythronate 4-phosphate dehydrogenase and the corresponding nucleotide sequence (SMc00985 gene, PNAS 2001), which is 100%

identical to the nucleic acid sequence of SEQ ID NO: 1 of the instant application." (Paper No. 20060907 at 7).

The Examiner acknowledged, however, that Capela "do[es] not teach a process for producing vitamin B6." (*Id.*).

To fill the acknowledged gap in Capela, the Examiner relied on Yocum for "teach[ing] a process for producing pyridoxal or pyridoxine or vitamin B6 comprising a host cell, wherein [the] host cell is E. coli, comprising a PdxB gene (pyridoxine or vitamin B6 biosynthetic gene), which is ***very similar*** to PdxR gene of instant application." (*Id.* at 7-8) (emphasis added). The Examiner further asserted that Yocum "teach[es] cloning the gene in a vector, transforming E. coli as host cell and culturing the recombinant host cell, producing vitamin B6 and recovering from the culture." (*Id.* at 8).

The Examiner also acknowledged, however, that Yocum "do[es] not teach use of [the] PdxR gene from Sinorhizobium meliloti." (*Id.*).

The Examiner then contended that "[o]ne of the ordinary skilled in the art would have been motivated to isolate an erythronate 4-phosphate dehydrogenase gene from Sinorhizobium meliloti by searching PdxR homologous gene[s] of Yocum et al, by using BLAST search (global sequence homology search method) wherein the sequence of Capela et al. would have been recognized as a possible erythronate 4-phosphate dehydrogenase gene from Sinorhizobium meliloti, cloning said gene in [an] expression vector and transform[ing] the Sinorhizobium meliloti cell for over-producing vitamin B6 by over-producing erythronate 4-phosphate dehydrogenase protein." (*Id.*).

With a view toward furthering prosecution, we note that claim 1 (from which claim 2 depends) has been amended to recite "[a] process for the biological

production of vitamin B_6 which comprises cultivating a host cell transformed or transfected by an isolated DNA or by a vector or plasmid comprising the isolated DNA under conditions conducive to the production of vitamin B_6, and recovering vitamin B_6 from the culture, wherein the host cell is selected from Sinorhizobium or Escherichia and wherein the isolated DNA comprises a nucleotide sequence encoding PdxR, which is a flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase, selected from the group consisting of ...."

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine "***must be based on objective***

evidence of record." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added).

The rejection is devoid of *any* evidence in support of the proposed combination. All that is there is a conclusory statement that "[i]t has long been known that Sinorhizobium meliloti is an over-producer of vitamin B6" and [i]t would have been obvious to someone of ordinary skill ... [to] produce vitamin B6 more efficiently than [the] chemical method as taught by Yocum." (Paper No. 20060907 at 8). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Capela using Yocum to arrive at the claimed process. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of some motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based

upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)).

Assuming *arguendo* that Capela is properly combinable with Yocum, which it is not, such a combination would not suggest the currently claimed process. As acknowledged by the Examiner, Capela is silent about the use of the disclosed protein for vitamin B6 production. In filling this gap, the Examiner relies on Yocum, which is concerned with the production of vitamin B6 by overexpression of the PdxB gene of *E. coli*. However, the homology between the *E. coli* ***PdxB gene*** and the ***PdxR gene***, coding for the enzyme of the currently claimed invention, is in the range of ***only about 10%***, which is far from being "***very similar***" as asserted by the Examiner. (Paper No. 20060907 at 7-8). Thus, the Examiner's reasoning is simply flawed. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that ***the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references***.") (emphasis added). Here, the using of certain properties of the PdxR gene to motivate the Examiner's combination of the cited references in an attempt to arrive at the claimed process is based on an improper hindsight reconstruction of the claimed vitamin B6 process. Simply put, one of ordinary skill in the art using the sequence information of the *E. coli* PdxB gene of Yocum in a BLAST search would ***not*** be led to the PdxR gene of the

presently claimed process due to the extremely low amount of homology between the two sequences. Thus, the proposed combination falls short of filling the factual gap in Capela. For this reason also, the rejection should be withdrawn.

In addition, even if the Examiner's proposed combination is followed, the Examiner failed to identify the motivation to select the PdxR gene from among the BLAST results. As is well settled, a genus does not render obvious a species. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). Nor does the Examiner identify where the motivation comes from to make the necessary molecular modifications to go from the PdxB gene/polypeptide to the PdxR gene/polypeptide as recited. But that is precisely what the Examiner was required to do as recently reaffirmed by the Federal Circuit. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added). Thus, in the absence of any suggestion or motivation to select PdxR among the BLAST results, the rejection must fail for this reason as well.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 3 has also been rejected under 35 USC § 103 as being unpatentable over Capela and Capela II in view of Yocum and further in view of Tazoe *et al.* "Biosynthesis of Vitamin B_6 in *Rhizobium*: *In Vitro* Synthesis of Pyridoxine from 1-

Deoxy-D-xylulose and 4-Hydroxy-L-threonine," Biosci. Biotechnol. Biochem. 2002 Apr.; 66(4): 934-6). (Paper No. 20060907 at 8-9).

The rejection respectfully is traversed. At the outset we note that all arguments made in this paper concerning Capela, Capela II, and Yocum in the other §103 rejection are readopted and reasserted with respect to this rejection as if fully set forth here.

Capela is summarized above.

Capela II is summarized above.

Yocum is summarized above.

Tazoe discloses that "[p]yridoxine (vitamin B6) in *Rhizobium* is synthesized from 1-deoxy-D-xylulose and 4-hydroxy-L-threonine." (Page 934). Tazoe further discloses that to "define the pathway enzymatically, ... an enzyme reaction system with a crude enzyme solution of *R. meliloti* IFO14782" had to be established. (*Id.*). "The enzyme reaction system required NAD+, NADP+, and ATP as coenzymes, and differed from the *E. coli* enzyme reaction system comprising PdxA and PdxJ proteins, which requires only NAD+ for formation of pyridoxine 5'-phosphate from 1-deoxy-D-xylulose 5-phosphate and 4-(phosphohydroxy)-L-threonine." (*Id.*).

In making the rejection, the Examiner asserted that Capela discloses "a putative oxidoreductase protein, which is 100% identical to SEQ ID NO: 2 of the instant application, inherently a erythronate4-phosphate dehydrogenase and the corresponding nucleotide sequence (SMc00985 gene, PNAS 2001), which is 100% identical to the nucleic acid sequence of SEQ ID NO: 1 of the instant application." (Paper No. 20060907 at 9).

The Examiner acknowledged, however, that Capela "do[es] not teach a process for producing vitamin B6." (*Id.*).

To fill the acknowledged gap in Capela, the Examiner relied on Yocum for "teach[ing] a process for producing pyridoxal or pyridoxine or vitamin B6 comprising a host cell, wherein host cell is E. coli, comprising a PdxB gene (pyridoxine or vitamin B6 biosynthetic gene), which is ***very similar*** to PdxR gene of instant application, culturing the recombinant host cell, producing vitamin B6 and recovering from the culture." (*Id.*) (emphasis added).

The Examiner also acknowledged, however, that Yocum "do[es] not teach [the] use of Sinorhizobium as a transformed host cell for producing vitamin B6." (*Id.*).

To fill this further acknowledged gap, the Examiner relied on Tazoe for "teach[ing] vitamin B6 over-production in Rhizobium (Sinorhizobium) from 1-deoxy-D-xylulose and 4-hydroxy-L-threonine as substrates." (*Id.*). The Examiner further asserted that Tazoe "also teach[es] an enzyme reaction system with a crude enzyme solution of R. meliloti IFO14782 with NAD+, NADP+, and ATP as coenzymes for biological production of vitamin B6." (*Id.*).

The Examiner then contended that "[i]t has long been known that Sinorhizobium (Rhizobium) meliloti is an over-producer of vitamin B6 (constitutively)" and Yocum "clearly show[s] that erythronate 4-phosphate dehydrogenase (PdxB) from E. coli can efficiently produce vitamin B6 in transformed E. coli cells." (*Id.* at 9-10). Therefore, "[o]ne of [ ] ordinary skill[ ] in the art would have been motivated to use [a] transformed Sinorhizobium meliloti cell for the production of vitamin B6, which is known to over-produce vitamin B6 as taught by Tazoe et al. by transforming with [the]

erythronate 4-phosphate dehydrogenase gene of Capela et al. from Sinorhizobium meliloti for enhanced amount of vitamin B6 by the method of Yocum et al." (*Id.* at 10).

With a view toward furthering prosecution, we note that claim 1 (from which claim 3 depends) has been amended to recite "[a] process for the biological production of vitamin B_6 which comprises cultivating a host cell transformed or transfected by an isolated DNA or by a vector or plasmid comprising the isolated DNA under conditions conducive to the production of vitamin B_6, and recovering vitamin B_6 from the culture, wherein the host cell is selected from Sinorhizobium or Escherichia and wherein the isolated DNA comprises a nucleotide sequence encoding PdxR, which is a flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase, selected from the group consisting of ...."

As discussed above, it is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *Glaug*, 62 USPQ2d at 1152; *Oetiker*, 24 USPQ2d at 1444; and *Piasecki*, 223 USPQ at 788. If the PTO fails to meet its burden, then the applicant is entitled to a patent. *Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co.*, 127 S.Ct. at 1731-32 (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley*, 60 USPQ2d at 1008. Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is

well settled, the teaching, motivation, or suggestion to combine "***must be based on objective evidence of record***." *Lee*, 61 USPQ2d at 1433 (emphasis added).

This rejection, like the previous one, is also devoid of *any* evidence in support of the proposed combination. All that is there is a conclusory statement that "[o]ne of [ ] ordinary skill[ ] in the art would have been motivated to use [a] transformed Sinorhizobium meliloti cell for the production of vitamin B6, which is known to over-produce vitamin B6 as taught by Tazoe et al. by transforming with erythronate 4-phosphate dehydrogenase gene of Capela et al. from Sinorhizobium meliloti for enhanced amount of vitamin B6 by the method of Yocum." (Paper No. 20060907 at 10). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Capela using Yocum and then Tazoe to arrive at the claimed process. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of some motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing

so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)).

Assuming *arguendo* that Capela is properly combinable with Yocum and Tazoe, which it is not, such a combination would not suggest the currently claimed process. As acknowledged by the Examiner, Capela is silent about the use of the disclosed protein for vitamin B6 production. In filling this gap, the Examiner relies on Yocum, which is concerned with the production of vitamin B6 by overexpression of the PdxB gene of *E. coli*. However, as stated above, the homology between the *E. coli* ***PdxB gene*** and the ***PdxR gene***, coding for the enzyme of the currently claimed invention, is in the range of ***only about 10%***, which is far from being "***very similar***" as asserted by the Examiner. (Paper No. 20060907 at 9). Thus, the Examiner's reasoning remains flawed. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that ***the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references***.") (emphasis added). Here, the using of certain properties of the PdxR gene to motivate the Examiner's combination of the cited references in an attempt to arrive at the claimed process is based on an improper hindsight reconstruction of the

claimed vitamin B6 process. Simply put, one of ordinary skill in the art using the sequence information of the *E. coli* PdxB gene of Yocum in a BLAST search would ***not*** be led to the PdxR gene of the presently claimed process due to the extremely low amount of homology between the two sequences. Thus, the proposed combination falls short of filling the factual gap in Capela. For this reason also, the rejection should be withdrawn.

In addition, even if the Examiner's proposed combination is followed, the Examiner failed to identify the motivation to select the PdxR gene from among the BLAST results. As is well settled, a genus does not render obvious a species. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). Nor does the Examiner identify where the motivation comes from to make the necessary molecular modifications to go from the PdxB gene/polypeptide to the PdxR gene/polypeptide as recited. But that is precisely what the Examiner was required to do as recently reaffirmed by the Federal Circuit. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added). Thus, in the absence of any suggestion or motivation to select PdxR among the BLAST results, the rejection must fail for this reason as well.

Unfortunately for the Examiner, Tazoe does not fill the factual gaps left by Yocum. The enzymatic pathway disclosed in Tazoe fails to disclose or suggest the PdxR gene of the presently claimed process. The described enzymatic pathway in

Tazoe is completely different - and has no relation to - the PdxR gene or enzymatic pathway described by the Applicants. As is well known, there are two pathways in *Sinorhizobium* for the production of vitamin B6 and in only one of them is the PdxR gene involved. (*See, e.g.,* Exhibit 1: Tazoe *et al.* "*Flavin Adenine Dinucleotide-Dependent 4-Phospho-D-Erythronate Dehydrogenase Is Responsible for the 4-Phosphohydroxy-L-Threonine Pathway in Vitamin B_6 Biosynthesis in Sinorhizobium meliloti*," J. Bacteriol., v. 188, no. 43, pp. 4635-4645 (2006)). The pathway utilizing PdxR, however, is not disclosed or suggested by Tazoe, and the Examiner has not even contended otherwise. Thus, for this further reason, the rejection should be withdrawn.

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

For the foregoing reasons, favorable action on the merits, including entry of the amendments, withdrawal of the objections and rejections, and allowance of all the claims, respectfully is requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box. 1450 Alexandria, VA 22313-1450, on July 18, 2007.

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